Evaluation of clinical efficacy of tumor necrosis factor-α inhibitors in treatment of distal extremity swelling with pitting edema in psoriatic arthritis of inadequate response to conventional therapy: A 10-year retrospective study

CHENYANG ZHAO[1], BINGQIAN LIU[1], YUAN YAO[1], KEVIN YANG[1,2], BO ZANG[1] and BIN LIU[1]

[1]Department of Rheumatology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266003, P.R. China; [2]Faculty of Medicine, Lund University, 22002 Lund, Sweden

Received January 16, 2023; Accepted March 31, 2023

DOI: 10.3892/etm.2023.11962

Abstract. Distal extremity swelling with pitting edema in psoriatic arthritis (PsA) is a rare rheumatological condition, whose management presents a challenge. The aim of the present study was to identify the clinical characteristics of, and formulate a standardized management strategy for, patients with distal extremity swelling with pitting edema in PsA. The medical records of consecutive patients with PsA, with or without distal extremity swelling with pitting edema, were systematically analyzed over a ~10-year period (between September 2008 and September 2018) in a single center and a comprehensive review (pathogenic mechanisms, clinical manifestations, and treatments) was undertaken. A total of 167 patients with PsA were evaluated, and distal extremity swelling with pitting edema was recorded in 16 of these patients. In three of the 16 patients, distal extremity swelling with pitting edema occurred as the first, isolated manifestation of PsA. The upper and lower extremities were affected, predominantly asymmetrically. Female patients with PsA were more likely to be affected with pitting edema and the blood test results revealed that the patients with PsA and pitting edema also presented with a significantly higher erythrocyte sedimentation rate and concentration of C-reactive protein. The onset of pitting edema was associated with the activity of the disease. Lymphoscintigraphy and magnetic resonance imaging (MRI) scans revealed that edema might have resulted from inflammation of the tenosynovial structures. Furthermore, treatment with tumor necrosis factor-α inhibitor (TNFi) elicited improvements in patients with pitting edema that were not responsive to conventional synthetic disease-modifying antirheumatic drug therapy. In conclusion, distal extremity swelling with pitting edema, also termed atypical remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, may represent the initial isolated manifestation of PsA. The atypical RS3PE syndrome in PsA was attributable to inflammation of the tenosynovial structures, and TNFi may serve as a potential treatment.

Correspondence to: Dr Bin Liu, Department of Rheumatology, The Affiliated Hospital of Qingdao University, 16 Jiang Su Lu, Shi Nan, Qingdao, Shandong 266003, P.R. China
E-mail: binliu72314@163.com

Abbreviations: bDMARD, biologic disease modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28, Disease Activity Score using 28 joint counts; ESR, erythrocyte sedimentation rate; ETN, etanercept; MMP, matrix metalloproteinase; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RS3PE, remitting seronegative symmetrical synovitis with pitting edema; SSZ, sulfasalazine; TGF-β, transforming growth factor-β; TNFi, tumor necrosis factor-α inhibitor; VEGF, vascular endothelial growth factor

Key words: psoriatic arthritis, pitting edema, tumor necrosis factor-α inhibitor

Introduction

Distal extremity swelling with pitting edema, also termed remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, is a well-recognized extra-articular feature of rheumatoid arthritis (RA), first described by Kalliomaki and Vastamaki in 1968 (1), although its association with psoriatic arthritis (PsA) has been demonstrated to be atypical (2-9). Unlike RA with pitting edema, in PsA the upper limbs are the most common sites of involvement, with the right side being preferentially affected. Approximately half of the patients with PsA have bilateral edema; to the best of our knowledge, no correlation has been established between the severity of the arthritis and the characteristic features of pitting edema in PsA (3,8,10).

The management of RS3PE syndrome in patients with PsA presents a challenge. In the majority of cases, the introduction of, or a change in, conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy has been demonstrated not to result in any improvements in edema due to the underlying pathogenesis (11). A total of two main underlying mechanisms have been demonstrated to be associated with

RS3PE in patients with PsA: Defective lymphatic drainage and inflammation of the tenosynovial structures (5). Magnetic resonance imaging (MRI) scans and lymphoscintigraphy are used to differentiate between the two different mechanisms, thus, these techniques may be of therapeutic value (5). Inflammation of the tenosynovial structures has been demonstrated to respond well to csDMARD therapy, whereas defects in the lymphatic vessels do not appear to be responsive (3). Biological (b) DMARDs have been established as a therapy for the treatment of rheumatic disorders and case reports have demonstrated the use of bDMARDs in the treatment of patients with PsA and pitting edema (10,12). The aim of the present study was to systematically analyze the medical data of patients with PsA, with or without RS3PE syndrome, from The Affiliated Hospital of Qingdao University (Qingdao, China).

Patients and methods

Patients. Medical charts of consecutive in- and outpatients with PsA admitted to The Affiliated Hospital of Qingdao University (Qingdao, China) between September 2008 and September 2018 were systematically analyzed, including demographic data, clinical features, laboratory findings (including blood tests) and treatment strategies, as well as the effectiveness of the treatment. PsA was diagnosed according to the criteria for the classification of PsA (13), and disease activity was evaluated according to the Disease Activity Score using 28 joint counts (DAS28) guidelines (14). The diagnosis of RS3PE syndrome was confirmed by diffuse unsymmetrical or symmetrical swelling of the upper or lower extremities, or both, usually distributed along a well-defined tenosynovial structure associated with pitting (15), at the time of admission or recorded in the chart of the patient. In patients with RS3PE syndrome, a color Doppler ultrasound was used to exclude venous or arterial occlusion and to evaluate the joints involved. Furthermore, quantitative ^{99m}Tc-labelled nanocolloid lymphoscintigraphy and MRI were performed on the affected sites to reveal the underlying mechanism. Patients with PsA that met both the inclusion and exclusion criteria were included in the present study. The inclusion criteria were as follows: i) Complete clinical data for the patient was available; and ii) the patient was aged ≥14 years, if the patient was aged <18 years, the consent of the patient's guardian was obtained). The exclusion criteria were as follows: i) History of alcohol, drugs or chemical abuse; ii) the patient had been previously diagnosed with cancer, primary or secondary immunodeficiency or other autoimmune disease; iii) venous or arterial occlusion was present and iv) incomplete clinical data was available for the patient.

The patients were prescribed sulfasalazine (SSZ; 2 g/day) and methotrexate (MTX; ≤15 mg/week), both in combination with non-steroidal anti-inflammatory drugs (NSAIDs; diclofenac sodium at a dose of 75 mg/day or celecoxib at a dose of 200 mg/day) to control the PsA. If the edema remained unchanged after 1 month following the aforementioned prescribed course of treatment, etanercept (ETN) was administrated subcutaneously at a dose of 50 mg/week. The present study was performed following approval by the Medical Ethics Committee of The Affiliated Hospital of Qingdao University (approval no. QYFY WZLL 23519). Written informed consent was obtained from all participants in the study.

Table I. Clinical features of patients with PsA with and without pitting edema.

Characteristic	Patients with PsA and pitting edema (n=16)	Patients with PsA without pitting edema (n=151)	P-value
Sex, female/male	11/5	57/94	0.016[a]
Mean age, years	53.8±9.1	50.7±14.1	0.324[b]
Mean duration of disease, years	8.8±2.6	10.2±1.4	0.012[b]
Mean ESR, mm/h	47.5±8.4	24.6±3.3	<0.001[b]
Mean CRP, mg/l	33.2±9.1	13.4±3.0	<0.001[b]
RF, +	1	11	1.000[a]
ACPA, +	0	10	0.600[a]
HLA B27, +	7	73	0.726[a]
Mean DAS28	5.3±1.3	3.0±0.9	<0.001[b]

Data are the mean ± SD, or n. [a]Differences between groups were compared using the χ^2 or Fisher's exact test. [b]Normally distributed outcomes were analyzed via two-tailed unpaired t-test. ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; DAS28, Disease Activity Score using 28 joint counts; ESR, erythrocyte sedimentation rate; HLA B27, human leukocyte antigen B27; RF, rheumatoid factor; PsA, psoriatic arthritis.

Statistical analysis. Data analysis was performed using SPSS 23.0 for Windows (IBM Corp.). Continuous data with a normal distribution are expressed as the mean ± standard deviation. To detect statistical differences in age, duration of disease, ESR, CRP and DAS28, two-tailed unpaired t-test was used. To detect statistical differences in sex and HLA B27, χ^2-test was used while Fisher's exact test was used for other characteristics. P<0.05 was considered to indicate a statistically significant difference.

Results

Differences between patients with PsA with and without pitting edema. A total of 167 patients with PsA were evaluated, comprising 99 men (59.3%) and 68 women (40.7%) with a mean age of 51.0±13.7 years (range, 14-86 years). Of the 167 patients with PsA, 16 (9.58%) also exhibited RS3PE syndrome during the course of the illness (Table I). Female patients were more likely to be affected with PsA and pitting edema compared PsA without pitting edema (68.8 vs. 36.3%). Blood test results revealed that patients with PsA and pitting edema presented with a significantly higher erythrocyte sedimentation rate (ESR) and concentration of C-reactive protein (CRP), as well as higher DAS28 score (a measure of disease activity in RA), compared with patients with PsA without pitting edema. The measurements of the three parameters for ESR, CRP and the DAS28 scores were 47.5±8.4 vs. 24.6±3.3 mm/h, 33.2±9.1 vs. 13.4±3.0 mg/l and 5.3±1.3 vs. 3±0.9 for patients with PsA with and without pitting edema, respectively.

Characteristics of patients with PsA and pitting edema. The present study included 16 patients with PsA (11 female

Table II. Clinical characteristics of 16 cases of psoriatic arthritis with pitting edema.

Case no.	Age, years	Sex	Localization of edema	Distribution of arthritis	Edema elimination time, days
1	48	M	Right upper limb	Spine and sacroiliac	6
2	63	F	Right lower limb	Spine, sacroiliac, hip, knee and ankle	9
3	57	F	Left lower limb	Spine, sacroiliac, hip and knee	10
4	65	M	Right upper limb	Sacroiliac, DIP, PIP, MCP, elbow, wrist and knee	14
5	42	M	Right upper limb	Spine, DIP, MCP, elbow, knee and ankle	7
6	55	F	Right upper limb	Spine, sacroiliac, knee, ankle, DTP and PTP	14
7	38	F	Right upper limb	Spine, DIP, PIP, MCP, wrist, ankle and DTP	7
8	52	F	Right upper limb	Sacroiliac, DIP, elbow, knee, MTP, PTP and DTP	12
9	55	M	Bilateral lower limb	Elbow, knee, ankle and heel	14[a]
10	66	F	Right upper limb	Spine, knee, MTP and PTP	15
11	56	M	Right upper limb	Spine, DIP, elbow and knee	20
12	43	F	Bilateral upper limb	Sacroiliac, PIP, MCP, MTP and PTP	14
13	46	F	Left lower limb	Spine, DIP, elbow, knee, ankle and heel	14
14	59	F	Right upper limb	DIP, PIP, MCP, knee, MTP and PTP	11
15	68	F	Left upper limb	Spine, DIP, PIP, MCP and knee	8
16	48	F	Right hand	Spine, PIP and MCP	7

[a]Symptoms reappeared following cessation of therapy. DIP, distal interphalangeal; DTP, distal phalanx of a toe; M, male; F, female; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; PTP, proximal phalanx of a toe.

and 5 male) and pitting edema (Table II). The mean age of the patients was 53.81±9.1 years (range, 38-68 years), and the mean duration of the disease was 8.81±10.2 years (range, 1-36 years). The onset of pitting edema was associated with the disease activity of PsA. In patients with PsA and pitting edema, the upper extremities were the most common sites of involvement (12/16 patients), with the right side (11/16 patients) being preferentially affected, and the lower extremities were involved in 5 (27.8%) episodes (Fig. 1). The involvement of extremities was bilateral in 2 (12.5%) episodes, and unilateral in 14 (87.5%) episodes. The involvement of upper extremities was symmetrical-bilateral in 1 (7.7%) episode, and asymmetrical in 12 (92.3%) episodes. Finally, lower extremities were bilaterally affected in 1 (20%) episode and unilaterally affected in 4 (80%) episodes.

All patients with PsA and pitting edema were examined using ultrasound, MRI scans and lymphoscintigraphy, which revealed that the associated edema might have been caused by inflammation of the tenosynovial structures and normal lymphatic drainage (Fig. 2).

Figure 1. Marked psoriatic rash and swelling with pitting edema, affecting the L hand and forearm. L, left; R, right.

Management of patients with PsA and pitting edema. During the course of treatment with NSAIDs SSZ and MTX, 10 patients with PsA experienced RS3PE syndrome. Following administration of ETN at a dose of 50 mg/week, the edema went into complete remission within 2 weeks. For three patients where the features and symptoms of PsA developed concurrently with RS3PE syndrome, after having been prescribed with NSAIDs for 1 month, the symptoms of PsA went into partial remission, but this therapy failed to adequately control edema. Subsequently, ETN was administered at a dose of 50 mg/week and the symptoms of edema were eliminated after 6-15 days. In 3/16 (18.8%) of the patients (all female), RS3PE syndrome presented as a first, isolated manifestation of PsA. These patients were treated with NSAIDs for a period of 1 month without any effect on the edema; after this time, ETN was administered subcutaneously at a dose of 50 mg/week. The episodes of edema were relieved after 7-21 days; however, the symptoms of arthritis were only modestly improved after 1 month. In one patient, the episodes of distal swelling with pitting edema went into relapse after the therapy had been stopped (Fig. 3).

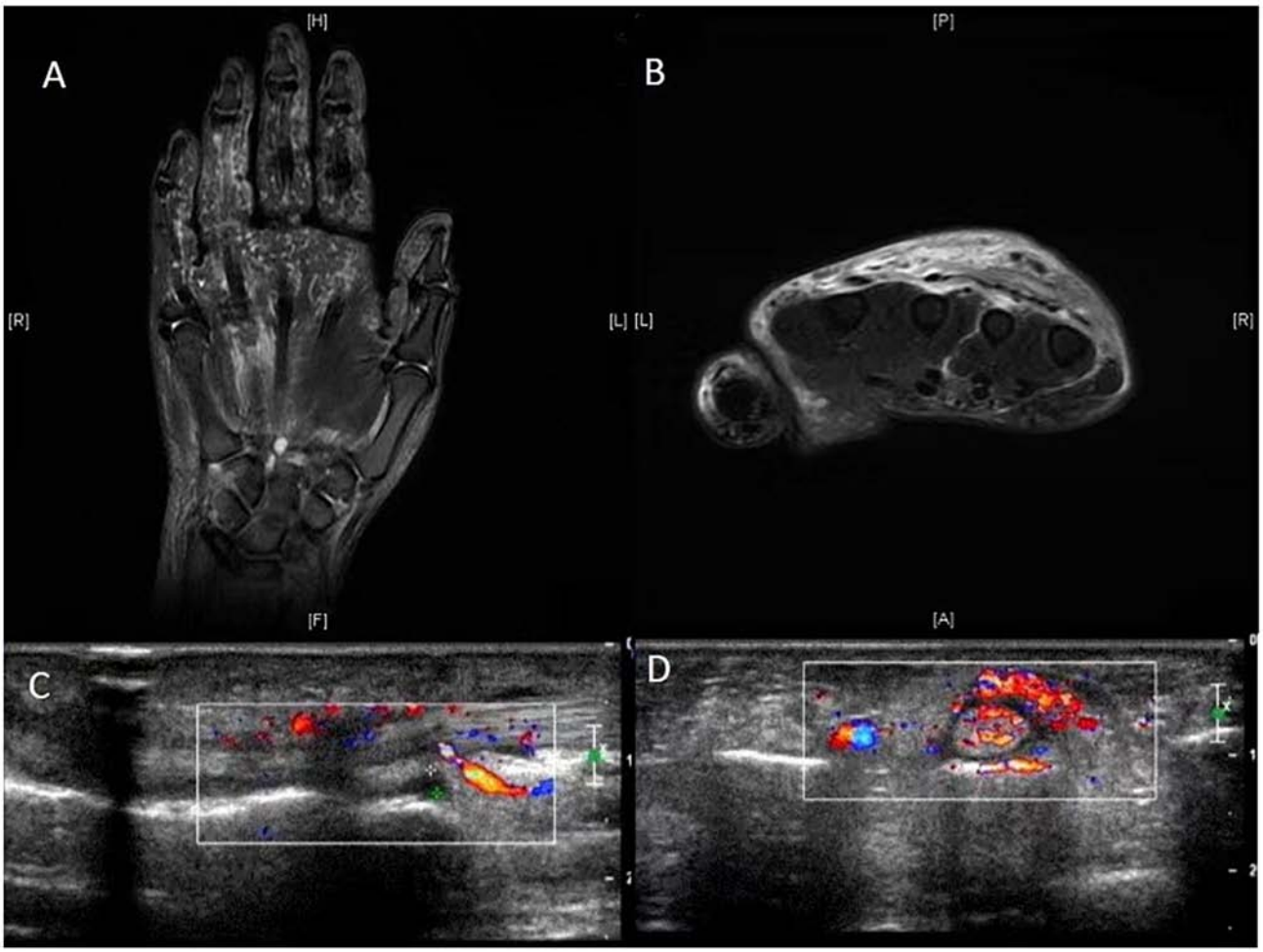

Figure 2. MRI and ultrasound of the hand in patients with PsA and RS3PE. MRI (A) coronal view revealing swelling of subcutaneous soft tissue of the back of the hand and fingers, marked by diffuse strips of fat suppressed T2WI on the ring finger and (B) transverse view revealing diffuse edema at the proximal metacarpal. The subcutaneous soft tissue on the back of the hand was clearly swollen. Ultrasound revealing (C) subcutaneous soft tissue swelling on the back of the hand with an uneven internal echo and (D) annular hypoechoic area around the extensor tendon, indicating subcutaneous soft tissue swelling and an uneven internal echo. MRI, magnetic resonance imaging; R, right; H, head; L, left; P, posterior; F, foot; A, anterior; T2WI, T2-weighted imaging.

All patients with PsA and RS3PE syndrome were available for follow-up and completed a 4-year follow-up; no malignancy was detected in any of these patients (Fig. 3).

Discussion

PsA is an inflammatory rheumatic disorder with unknown etiology and a heterogeneous clinical spectrum of symptoms. The prevalence rates of PsA (after 1987 until December 2006) varied between 0.001% (Japan) to 0.42% (Italian), and was characterized by having arthritis in association with psoriasis (16). In certain patients, psoriasis is associated with arthritis (5-42% of patients) (17). Nearly 15% of patients with PsA experience onset of arthritis prior to the onset of psoriasis (18). PsA belongs to a group of conditions collectively termed spondyloarthritis. A total of five conditions have been defined: Mono- or oligoarticular, polyarticular, distal interphalangeal joint predominant disease, axial disease with or without associated peripheral arthritis and arthritis mutilans (19).

Regarding the immunopathogenesis of RS3PE syndrome, TNF-α exerts a role in cartilage degradation via promotion of the production of matrix metalloproteinases (MMPs), which induces cartilage erosion and increases the expression of both vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) (20). VEGF and TGF β are more highly expressed in PsA synovium, thus illustrating the increased vascularity with a representational winding of the vascular bed of PsA synovium with respect to RA (21,22). Within the joint, TNF-α overexpression induces increased production of MMPs and cartilage destruction, thereby causing abnormal bone remodeling that is a characteristic feature of PsA.

RS3PE syndrome is a non-specific clinical feature occurring in a broad spectrum of disorders with an incidence rate of ~0.09% in the elderly (age ≥60 years), with a higher rate of onset in males compared with females (23,24). Retrospective and perspective studies have indicated that the mean prevalence rate of cancer in RS3PE syndrome is 20% (15,25-27). In the present study, RS3PE syndrome was observed in 16 patients with PsA, who were followed up for at least 4 years, and no malignancy was discovered. Other than neoplasms, various types of rheumatic disease (e.g. Sjögren's syndrome, ankylosing spondylitis, reactive arthritis, polymyalgia rheumatica, sarcoidosis etc.) occurring in RS3PE syndrome have been reported (28-32). To date, only a limited number of studies have been published on PsA and

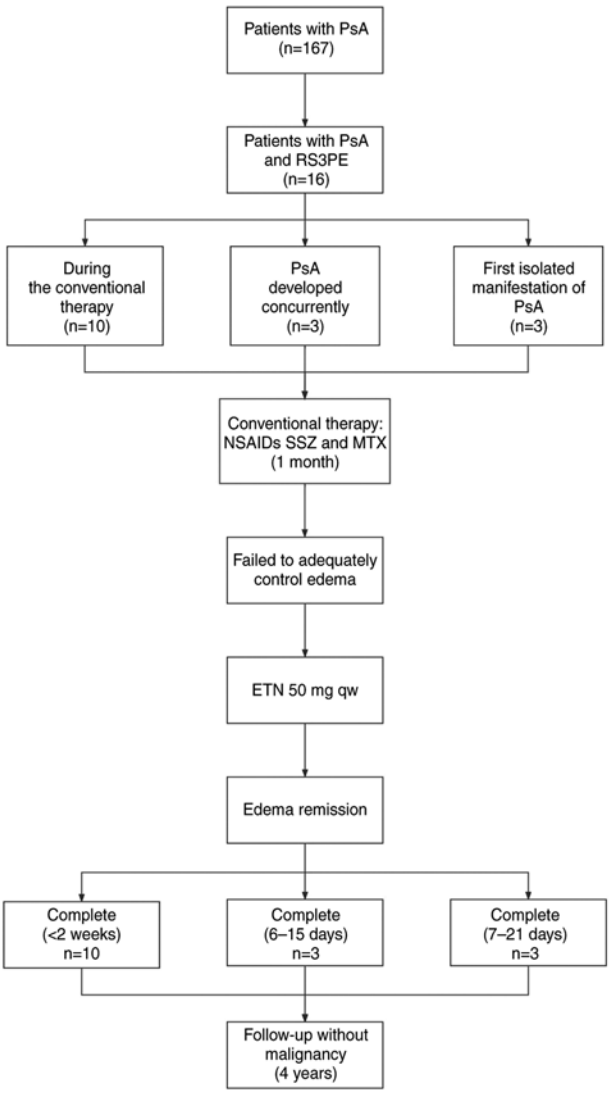

Figure 3. Study flow diagram of tumor necrosis factor-α inhibitors in treatment of patients with PsA and RS3PE of inadequate response to conventional therapy. PsA, psoriatic arthritis; RS3PE, remitting seronegative symmetrical synovitis with pitting edema; NSAID, non-steroidal anti-inflammatory drug; SSZ, sulfasalazine; MTX, methotrexate; ETN, etanercept; qw, once-weekly.

RS3PE syndrome (2-9). One case-control study (33) demonstrated that 21% of patients with PsA have RS3PE syndrome; furthermore, in 20% of patients, this feature is the first presentation of PsA, edema is unilateral, and the lower extremities are most commonly involved (33). In the present case series, 9.6% of patients with PsA exhibited RS3PE syndrome; for 18.8% of the patients with this feature, it presented as the first, isolated manifestation of PsA. Furthermore, onset of pitting edema was associated with disease activity and the upper extremities were predominantly asymmetrically affected in the present study (Tables I and II). This different distribution of edema compared with another case-control study might be explained by the choice of cases, and the difference of ethnicity (Asian vs. Caucasian populations with RS3PE with vs. without PsA) (23). The present study hypothesized that edema in patients with PsA may be considered as an atypical RS3PE syndrome, since it is mainly unilateral and predominantly involves the upper limbs, rather than the lower limbs (28).

Two different pathogenic mechanisms causing RS3PE syndrome in patients with PsA have been proposed (5,9). As aforementioned, VEGF and TNF-α have a role in the immunopathogenesis of PsA, and these pro-inflammatory molecules may contribute to development of atypical RS3PE syndrome in patients with PsA (21). VEGF has a vasodilatory effect, leading to an increase in vasopermeability (34), which has an essential role in development of the RS3PE syndrome (35). It has been postulated that neoplasia, other rheumatic disease (e.g. polymyalgia rheumatica and giant cell arteritis) and drugs (e.g. Tirofiban) might result in the production of VEGF and other molecules (e.g. tumor necrosis factor-α), which promote polyarthritis/polysynovitis and subcutaneous pitting edema of the extremities (15,17,36).

MRI, ultrasound and lymphoscintigraphy are used to reveal the underlying mechanisms of RS3PE syndrome as the inflammation of tenosynovial structures is responsive to therapy, whereas the lymphatic vessels are unresponsive to pharmacological treatment (9). MRI is able to discern inflammatory changes within peripheral joints, tendons sheaths and entheses that occur early in inflammatory changes. Furthermore, MRI is used to evaluate inflammation of the sacroiliac joints and the spine. Compared with radiographs, MRI is more sensitive in being able to detect early structural damage. Therefore, it is a useful technique for detecting disease activity, differential diagnosis and supporting the therapeutic decision-making processes (37). Doppler ultrasound has been validated less for PsA compared with for RA (37). Ultrasound may be used to identify and investigate enthesitis, joint effusions, synovial proliferation and erosions. It may also be used to exclude venous or arterial occlusion-induced edema. Through detecting hyperemia, ultrasound indirectly reveals inflammation and differentiates acute synovial proliferation from effusion (38). Ultrasound and MRI studies have been useful in demonstrating subcutaneous edema and tenosynovitis, as well as in detecting joint involvement at an early stage (37,38). However, unlike these techniques, lymphoscintigraphy offers an objective and reliable approach to diagnosing and characterizing the severity of lymphedema, which is difficult to diagnose, especially in its early stages. On the basis of the lymphoscintigraphic image pattern, it is possible to determine whether the limb swelling is due to lymphedema (39). In the present study, through the use of ultrasound, MRI scans and lymphoscintigraphy, it was possible to demonstrate that the patients with PsA and edema had edema that may have been caused by inflammation of the tenosynovial structures, rather than defective lymphatic drainage.

The management of RS3PE syndrome in patients with PSA has not yet been standardized. The use of systemic corticosteroids elicits a rapid response for patients with RS3PE syndrome, although these drugs should be used with caution in patients with PsA, as withdrawal may trigger a relapse of psoriasis (12,40). csDMARDs are effective in treating peripheral PsA, but were do not effectively treat RS3PE syndrome (6); this is consistent with results of the present study. Previous studies have provided evidence for the efficacy of bDMARDs to control the symptoms of PsA, and to either impede or arrest radiological disease progression (12,41). In addition, case reports have previously been published regarding the use of bDMARDs as a therapy for patients with PsA and pitting edema (10,12). The present study suggested that ETN might be

used to treat the atypical RS3PE syndrome that was resistant to csDMARD management in patients with PsA.

However, there were a number of limitations associated with the present study. Firstly, the present study was a single-center study, so it was difficult to avoid the problem of small sample size. In the future, multi-center studies with large sample sizes should be conducted. Inclusion of other ethnic groups and regions should be considered in future studies to validate the results of the present study. At the same time, prospective studies should be performed. Given that the precise mechanism of pathogenesis of PsA has yet to be fully elucidated, future research should investigate other kinds of biological agent for treatment of distal extremity swelling with pitting edema in patients with PSA that responds inadequately to conventional therapy. Future advances in genetic analysis and targeted therapies may facilitate genetic and immune profile modification therapies.

In conclusion, distal extremity swelling with pitting edema in patients with PsA is an atypical RS3PE syndrome that may be initially apparent as a symptom of PsA. TNFi may be an effective treatment.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant nos. 81241094 and 81671600) and The Natural Science Foundation of Shandong Province (grant no. ZR2016HM13).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CZ conceived and designed the study and wrote the manuscript. BingL, YY and KY analyzed and interpreted data for the work. BZ performed the investigation. BinL contributed to study design and interpretation of data and edited the manuscript. BingL and BinL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted following approval by the Medical Ethics Committee of The Affiliated Hospital of Qingdao University (approval no. QYFY WZLL 23519).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kalliomaki JL and Vastamaki M: Chronic diffuse oedema of the rheumatoid hand: A sign of local lymphatic involvement. Ann Rheum Dis 27: 167-169, 1968.
2. Salvarani C, Macchioni PL, Veneziani M, Rossi F, Lodi L, Baricchi R, Boiardi L and Portioli I: Upper limb lymphedema in psoriatic arthritis. J Rheumatol 17: 273-274, 1990.
3. Mulherin DM, FitzGerald O and Bresnihan B: Lymphedema of the upper limb in patients with psoriatic arthritis. Semin Arthritis Rheum 22: 350-356, 1993.
4. Kiely PD, Bland JM, Joseph AE, Mortimer PS and Bourke BE: Upper limb lymphatic function in inflammatory arthritis. J Rheumatol 22: 214-217, 1995.
5. Salvarani C, Cantini F, Olivieri I, Niccoli L, Senesi C, Macchioni L, Boiardi L and Padula A: Distal extremity swelling with pitting edema in psoriatic arthritis: Evidence of 2 pathological mechanisms. J Rheumatol 26: 1831-1834, 1999.
6. Bohm M, Riemann B, Luger TA and Bonsmann G: Bilateral upper limb lymphoedema associated with psoriatic arthritis: A case report and review of the literature. Br J Dermatol 143: 1297-1301, 2000.
7. Diez-Porres L, Munoz-Fernandez S, Aguado P, Alonso M and Martin-Mola E: Remitting seronegative symmetrical synovitis with pitting oedema as the first manifestation of psoriatic arthropathy. Rheumatology (Oxford) 41: 1333-1335, 2002.
8. Yamamoto T and Nishioka K: Psoriasis arthropathy and lymphedema. J Dermatol 29: 812-814, 2002.
9. Quarta L, Corrado A, d'Onofrio F, Maruotti N and Cantatore FP: Two cases of distal extremity swelling with pitting oedema in psoriatic arthritis: The different pathological mechanisms. Rheumatol Int 30: 1367-1370, 2010.
10. Almodovar R, Zarco P, Quiros FJ and Mazzucchelli R: Infliximab treatment efficacy in lymphoedema associated with ankylosing spondylitis. Rheumatology (Oxford) 43: 1456, 2004.
11. Lubrano E, Perrotta FM, Scriffignano S, Coates LC and Helliwell P: Sustained very low disease activity and remission in psoriatic arthritis patients. Rheumatol Ther 6: 521-528, 2019.
12. Lekpa FK, Economu-Dubosc A, Fevre C, Claudepierre P and Chevalier X: Efficacy of etanercept in lymphedema associated with psoriatic arthritis. J Rheumatol 36: 207-208, 2009.
13. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H and Group CS: Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. Arthritis Rheum 54: 2665-2673, 2006.
14. Helliwell PS, FitzGerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, McHugh N, Mease PJ, Strand V, Waxman R, *et al*: The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis 72: 986-991, 2013.
15. Gan Y, Sun Y, Jin J, Wang Y, Chen J, Chung Y, Li X and Ye H: bFGF could be a biomarker of malignancy in RS_3PE syndrome: An ambispective single-center cohort analysis of 51 patients. Arthritis Res Ther 23: 261, 2021.
16. Kerschbaumer A, Fenzl KH, Erlacher L and Aletaha D: An overview of psoriatic arthritis-epidemiology, clinical features, pathophysiology and novel treatment targets. Wien Klin Wochenschr 128: 791-795, 2016.
17. Gladman DD and Brockbank J: Psoriatic arthritis. Expert Opin Investig Drugs 9: 1511-1522, 2000.
18. Gottlieb AB, Bakewell C and Merola JF: Musculoskeletal imaging for dermatologists: Techniques in the diagnosis and management of psoriatic arthritis. Dermatol Ther (Heidelb) 11: 1199-1216, 2021.
19. Szczerkowska-Dobosz A, Krasowska D, Bartosinska J, StawczykMacieja M, Walczak A, Owczarczyk-Saczonek A, Reich A, Batycka-Baran A, Czajkowski R, Dobrucki IT, *et al*: Pathogenesis of psoriasis in the 'omic' era. Part IV. Epidemiology, genetics, immunopathogenesis, clinical manifestation and treatment of psoriatic arthritis. Postepy Dermatol Alergol 37: 625-634, 2020.
20. Kenzaka T: The relationship between remitting seronegative symmetrical synovitis with pitting edema and vascular endothelial growth factor and matrix metalloproteinase 3. Intern Med 59: 1021-1022, 2020.
21. Fearon U, Griosios K, Fraser A, Reece R, Emery P, Jones PF and Veale DJ: Angiopoietins, growth factors, and vascular morphology in early arthritis. J Rheumatol 30: 260-268, 2003.
22. Veale DJ and Fearon U: The pathogenesis of psoriatic arthritis. Lancet 391: 2273-2284, 2018.

23. Bucaloiu ID, Olenginski TP and Harrington TM: Remitting seronegative symmetrical synovitis with pitting edema syndrome in a rural tertiary care practice: A retrospective analysis. Mayo Clin Proc 82: 1510-1515, 2007.
24. Kimura M, Tokuda Y, Oshiawa H, Yoshida K, Utsunomiya M, Kobayashi T, Deshpande GA, Matsui K and Kishimoto M: Clinical characteristics of patients with remitting seronegative symmetrical synovitis with pitting edema compared to patients with pure polymyalgia rheumatica. J Rheumatol 39: 148-153, 2012.
25. Gisserot O, Cremades S, Landais C, Leyral G, Bernard P and de Jaureguiberry JP: RS3PE revealing recurrent non-Hodgkin's lymphoma. Joint Bone Spine 71: 424-426, 2004.
26. Chiappetta N and Gruber B: Remitting seronegative symmetrical synovitis with pitting edema associated with acute myeloid leukemia. J Rheumatol 32: 1613-1614, 2005.
27. Tunc SE, Arslan C, Ayvacioglu NB, Sahin M, Akkus S and Yorgancigil H: Paraneoplastic remitting seronegative symmetrical synovitis with pitting edema (RS3PE syndrome): A report of two cases and review of the literature. Rheumatol Int 24: 234-237, 2004.
28. Schaeverbeke T, Fatout E, Marce S, Vernhes JP, Halle O, Antoine JF, Lequen L, Bannwarth B and Dehais J: Remitting seronegative symmetrical synovitis with pitting oedema: Disease or syndrome? Ann Rheum Dis 54: 681-684, 1995.
29. Olivieri I, Padula A, Favaro L, Pierro A, Oranges GS and Ferri S: Dactylitis with pitting oedema of the hand in longstanding ankylosing spondylitis. Clin Rheumatol 14: 701-704, 1995.
30. Cantini F, Niccoli L, Olivieri I, Barozzi L, Pavlica P, Bozza A, Macchioni PL, Padula AA and Salvarani C: Remitting distal lower extremity swelling with pitting oedema in acute sarcoidosis. Ann Rheum Dis 56: 565-566, 1997.
31. Okumura T, Tanno S, Ohhira M and Nozu T: The rate of polymyalgia rheumatica (PMR) and remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome in a clinic where primary care physicians are working in Japan. Rheumatol Int 32: 1695-1699, 2012.
32. Joseph AD, Kumanan T, Aravinthan N and Suganthan N: An unusual case of remitting seronegative symmetrical synovitis with pitting edema: Case report and literature review. SAGE Open Med Case Rep 8: 2050313X20910920, 2020.
33. Cantini F, Salvarani C, Olivieri I, Macchioni L, Niccoli L, Padula A, Falcone C, Boiardi L, Bozza A, Barozzi L and Pavlica P: Distal extremity swelling with pitting edema in psoriatic arthritis: A case-control study. Clin Exp Rheumatol 19: 291-296, 2001.
34. Ku DD, Zaleski JK, Liu S and Brock TA: Vascular endothelial growth factor induces EDRF-dependent relaxation in coronary arteries. Am J Physiol 265: H586-H592, 1993.
35. Arima K, Origuchi T, Tamai M, Iwanaga N, Izumi Y, Huang M, Tanaka F, Kamachi M, Aratake K, Nakamura H, *et al*: RS3PE syndrome presenting as vascular endothelial growth factor associated disorder. Ann Rheum Dis 64: 1653-1655, 2005.
36. Baumgartner I, Rauh G, Pieczek A, Wuensch D, Magner M, Kearney M, Schainfeld R and Isner JM: Lower-extremity edema associated with gene transfer of naked DNA encoding vascular endothelial growth factor. Ann Intern Med 132: 880-884, 2000.
37. Eder L, Aydin SZ, Kaeley GS, Maksymowych WP and Ostergaard M: Options for Assessing Joints and Entheses in Psoriatic Arthritis by Ultrasonography and Magnetic Resonance Imaging: How to Move Forward. J Rheumatol Suppl 94: 44-47, 2018.
38. Crespo-Rodriguez AM, Sanz Sanz J, Freites D, Rosales Z, Abasolo L and Arrazola J: Role of diagnostic imaging in psoriatic arthritis: How, when, and why. Insights Imaging 12: 121, 2021.
39. Szuba A, Shin WS, Strauss HW and Rockson S: The third circulation: Radionuclide lymphoscintigraphy in the evaluation of lymphedema. J Nucl Med 44: 43-57, 2003.
40. Kleinert S, Feuchtenberger M, Kneitz C and Tony HP: Psoriatic arthritis: Clinical spectrum and diagnostic procedures. Clin Dermatol 25: 519-523, 2007.
41. Kohm M, Burkhardt H and Behrens F: Anti-TNFalpha-therapy as an evidence-based treatment option for different clinical manifestations of psoriatic arthritis. Clin Exp Rheumatol 33 (Suppl 5): S109-S114, 2015.